Origins of the cardiovascular mortality epidemic in the United States, 1920–90

Steven Tate*

Andrew Noymer†,‡

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150-word abstract

During the twentieth century, as other causes of death declined, heart disease mortality increased in the United States. By 1958, the age-standardized death rate (ASDR) for cardiovascular causes for females was 1.84 times that for all other causes, *combined* (and 1.79× for males). Although contemporary observers believed that cardiovascular mortality would remain high, the late 1950s and early 1960s turned out to be the peak of what would be a roughly 70-year epidemic. By 1988 for females (1986 for males), a spectacular *volte-face* had been completed, with the ASDR for cardiovascular causes less than that for other causes combined. In addition to a thorough documentation of this phenomenon, this paper has two parts. First, we show that a prior imaginative hypothesis of Azambuja and Levins (2007) — that the 1918 influenza pandemic caused the cardiovascular mortality epidemic — is a poor match to the available data. Second, we advance an alternative hypothesis, that a combination of diet and, most especially, changes in the human microbiome wrought by the advent of penicillin and other antibiotics in the 1950s, was responsible for the main trends of cardiovascular mortality in the United States in the twentieth century.

*Pritzker School of Medicine, University of Chicago. tates@uchicago.edu

†Department of Population Health and Disease Prevention, University of California, Irvine

‡To whom correspondence should be addressed. University of California, 653 E Peltason Drive, Irvine CA 92697-3957, USA. noymer@uci.edu

Background

The idea that one disease or condition can affect outcomes after a long delay, and outcomes of other diseases, has a long pedigree (Derrick 1927; Kermack et al. 1934; Frost 1939; Merrell 1947; Kuh and Davey Smith 1993 discuss the history). This hypothesis has undergone a renaissance since the work of Barker and collaborators beginning in the 1980s (e.g. Barker and Osmond, 1986; Barker et al., 1989; Barker, 1990), which has spawned a huge literature. Comorbidity should not be circumscribed only to mean two or more illnesses in a given individual at a given point in time. When studying this phenomenon at the population level, the demographic concepts of age, period, and cohort (Hobcraft et al., 1982) can be exploited to test hypotheses. We illustrate this by considering Azambuja and Levins's (2007) provocative hypothesis that exposure to the 1918–19 'Spanish' influenza pandemic preconditioned later heart disease mortality.

The twentieth century witnessed a slow-burning but very deadly rise and fall of heart disease mortality, which has been expressly called an 'epidemic' (Marmot, 1992). This is in spite of the fact that ischaemic heart disease is 'chronic' — the antithesis of what is usually thought of as an epidemic disease. Azambuja and Levins's bold hypothesis uses comorbidity of the long-term type to explain the unusual chronic-disease epidemic. We demonstrate that age, period, cohort analysis yields no support for an influenza/heart disease nexus, however. We suggest instead that the twentieth century heart disease epidemic was caused by another sort of long-term comorbidity, using Grmek's (1969; 1989) pathocoenosis concept. We point to a confluence of bacterial (Nieto, 1998) and nutritional factors as being an explanation much more congruent with the medical-demographic data on the twentieth century heart disease mortality epidemic.

The 20th century slow epidemic of heart disease

Figure 1 shows the age-standardized death rate for heart disease (solid lines), 1900–2006, for the United States, for males and females. It also shows the age-standardized death rate for all other causes combined (dotted lines), excluding accidents, homicide, and suicide. Data sources are listed in the appendix, as well a breakdown of which ICD codes comprise heart disease. This figure compactly illustrates the long-term epidemic pattern of heart disease mortality in the United States in the twentieth century. The death rate for non-cardio mortality shows a consistent decline, 1900–1965 (punctuated

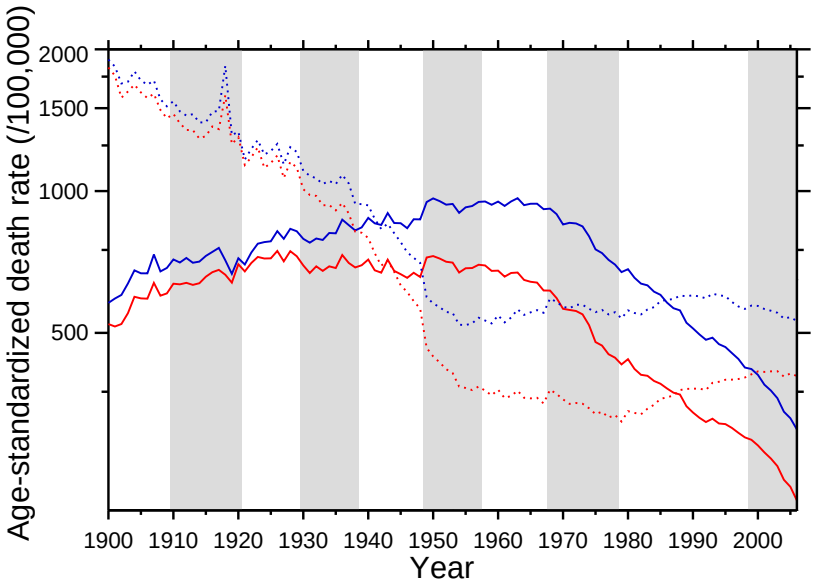

Figure 1: Age-standardized death rates, United States Death Registration Area (1900–32) and United States (1933–2006). Solid lines: heart disease; dotted lines: all other causes (see text for discussion). Males, blue; females, red. Rates calculated by the authors from data listed in the appendix. The alternating shaded regions mark changing regimes of disease classification, from ICD-1 to ICD-10.

by an increase associated with the 1918 influenza pandemic), followed by a plateau and slight increase, 1965–2006. On the other hand, heart disease mortality shows a slow increase through the late 1940s, followed by a plateau until the late 1960s, and a steep decline. Remarkably, from the early-1940s to the mid-1980s, the age-standardized death rate for cardiac causes exceed that for all other causes combined (excluding violent causes). Indeed, figure 1 underscores the fact that the continuing decline in nonviolent all-cause mortality in the last 30 years is driven by the decline in cardiac mortality.

Disaggregation: Age, period, cohort

A breakdown, by age, of heart disease mortality in the same time span, is presented in figure 2. The epidemic pattern described in figure 1 is present in ages 35 and above, and is more subtle when seen through the age-specific lens. The 1918 influenza pandemic imprints the heart disease data, especially for males, most strongly in age groups 15–24 and 25–34. Coincident with the pandemic, heart disease death rates go up, but then they fall steeply in 1919. For example, for men aged 25–34 the cardiac death rate fell from the highest value in the twentieth century in 1918, to the lowest value to date in the twentieth century, in 1919 (64.8 to 42.4 per 100,000). This has been characterized elsewhere (Noymer and Garenne 2000) as a harvesting effect, whereby those who perished in the 1918 flu (whether their deaths were recorded as influenza or not) were sicker than average, therefore making a healthier than average surviving population in 1919, with low death rates. The age groups responsible for the post-1920 rise in heart disease mortality are those 35 and older, above the age of peak impact of the 1918 influenza (cf. figure 3).

Post-1918 Period, not cohort, effects

The patterns in figure look like period, not cohort, effects. For example, the rise and subsequent fall in heart disease mortality in the 1920s and beyond, happens similarly (indeed, almost parallel) across age groups. Cohort effects characteristically occur with a delay caused by aging. For example, a cohort effect among those aged 20–24 in 1918 will be seen among those aged 30–34 in 1928 and those 40–44 in 1938. Parallel lines, are suggestive of period effects, with some factor(s) influencing several age groups in the same way at the same time.

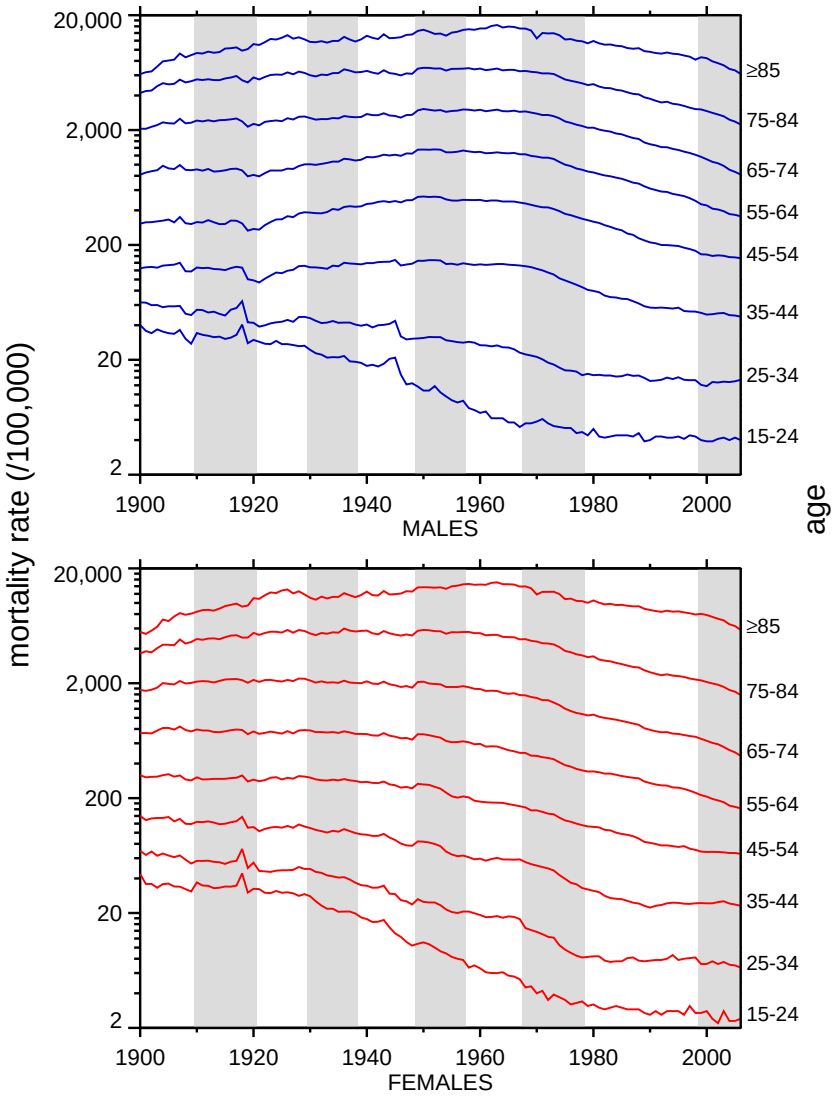

Figure 2: Heart disease age-specific death rates, United States Death Registration Area (1900–32) and United States (1933–2006). Males, top panel; females, bottom panel. Age groups are labeled on the right-hand vertical axes. Data sources and component causes listed in the appendix. The alternating shaded regions mark changing regimes of disease classification, from ICD-1 to ICD-10.

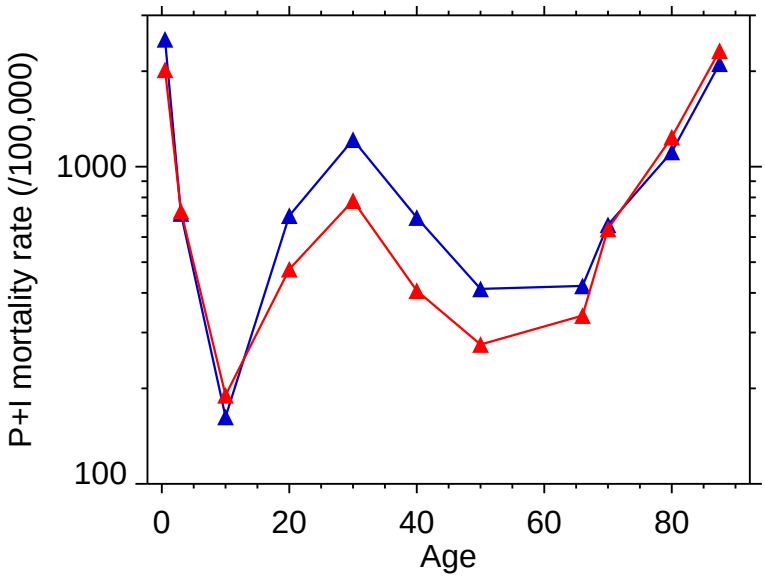

Figure 3: Pneumonia and influenza age-mortality profile, United States Death Registration Area, 1918. Males, blue; females, red. the right-hand vertical axes. Data from U.S. Department of Health, Education, and Welfare (1956).

males	25–34	35–44	45–54	55–64	65–74	75–84	≥85
15–24	1.97	1.16	1.32	0.71	1.14	0.02	0.14
25–34		4.09	2.63	2.06	1.25	0.92	0.75
35–44			5.04	4.15	4.18	3.85	2.93
45–54				6.76	5.17	4.85	4.33
55–64					7.10	5.93	4.95
65–74						8.00	5.76
75–84							6.91
females	25–34	35–44	45–54	55–64	65–74	75–84	≥85
15–24	2.23	2.26	1.79	1.94	1.62	0.85	0.04
25–34		4.79	3.67	1.53	2.11	1.77	0.27
35–44			5.94	4.82	4.38	4.04	2.79
45–54				5.36	5.94	6.06	3.31
55–64					6.15	6.74	4.86
65–74						7.73	6.08
75–84							5.96

Table 1: Goodman-Grunfeld test statistics for co-movement of data series in figure 2. The test statistics follow a normal distribution, so any number ≥1.96 can be regarded as significant at the 5% level in a two-sided test without adjustment for multiple comparisons.

To assess how much the lines in figure 2 are moving in parallel, we performed Goodman-Grunfeld tests for co-movement of time series with correction for serial correlation (Goodman and Grunfeld 1961). Table 1 shows the results of this test, with the diagonals showing strong evidence of co-movement between each series and the next-older one. Reading down each column, the final value (ie, the comparison with the adjacent age group) is always the strongest relationship.

With the exception of females, age 75–84, read

If not influenza, then what? A microbiome hypothesis

This section will propose an alternate hypothesis, that the (sur-)nutrition-infection-inflammation nexus is behind the long-term pattern of cardiovascular mortality in the twentieth century. Specifically, the advent of antibiotics in the 1950s (sulfa drugs in the 1930s, but these had a smaller impact)

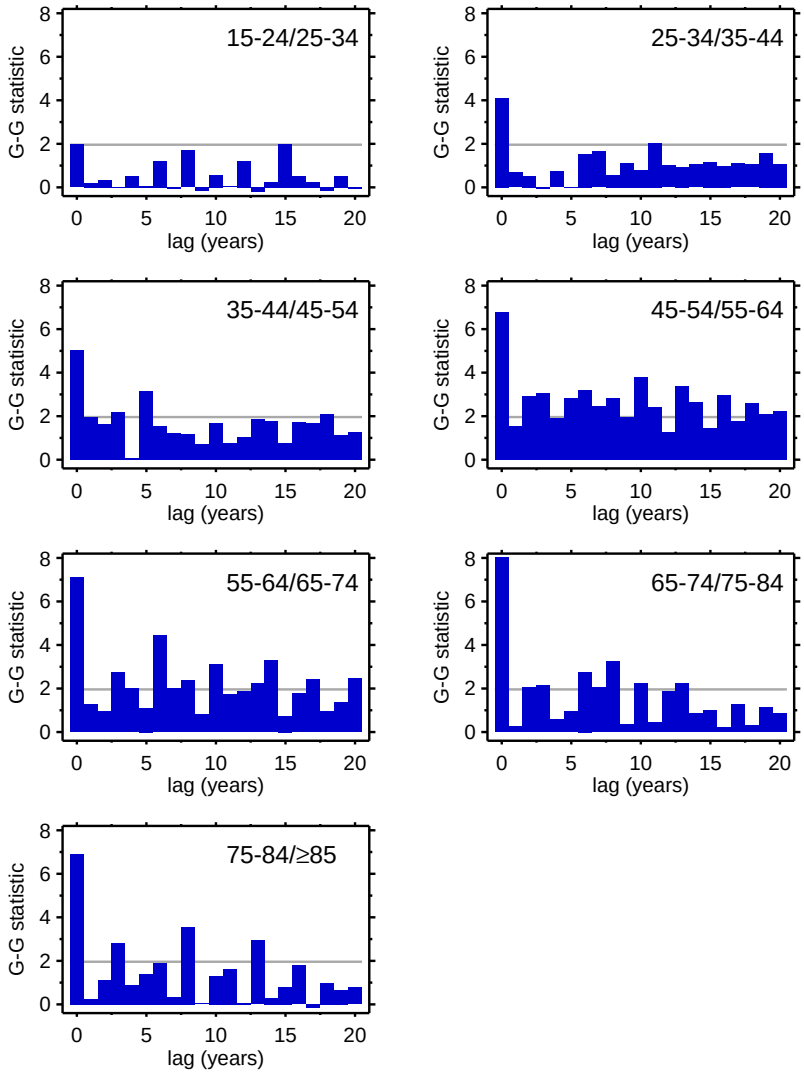

Figure 4: Figure caption

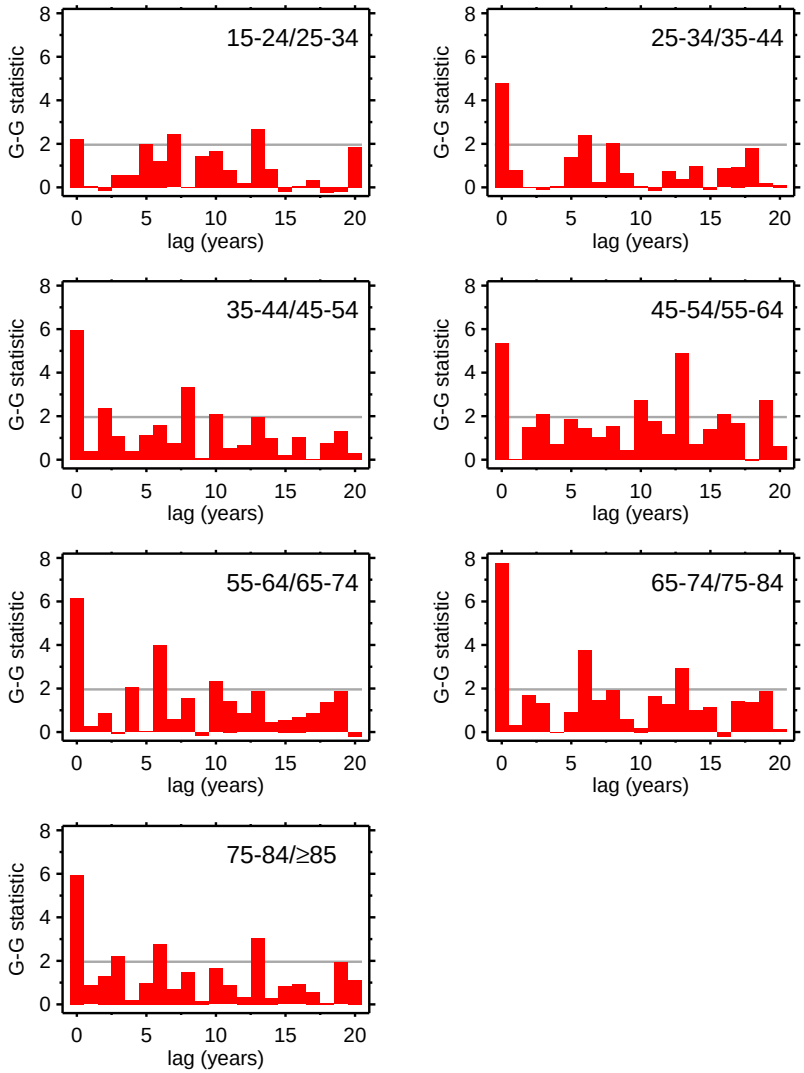

Figure 5: Figure caption

caused major changes in the human microbiome, that we are only now beginning to understand. We postulate that changes in nutrition are responsible for the rise of cardiovascular mortality, while changes in the human microbiome are responsible for the decline of cardiovascular mortality. This rise + fall combination is what lead to the epidemic patter of cardiovascular mortality, 1920–1990.

Conclusion

Under construction.

1. The hypothesis of Azambuja and Levins (2007) — that the 1918 influenza pandemic played a key role in the 20th century cardiovascular mortality epidemic — while admirably creative, is not congruent with available data.

2. The 20th century cardiovascular mortality epidemic is over-determined, but we suggest that changes in the human microbiome wrought by penicillin and other antibiotics can better account for the observed data.

Appendix: ICD codes for "heart disease"

Years	ICD	codes used	Source
1900–1909	1	47, 64–66, 77–86, 142	A
1910–1920	2	47, 64–66, 77–85, 142	A
1921–1929	3	51, 74, 75, 83, 87–90, 91b,c, 92–96, 151	A
1930–1938	4	56, 82, 90–95, 97–103	A
1939–1948	5	58, 83, 90–103	A
1949–1957	6	330–334, 400–468	A (1949–53); B (1954–57)
1958–1967	7	330–334, 400–468	B (1958–59); C (1960–67)
1968–1978	8	390–448	D
1979–1998	9	390–448	E
1999–2006	10	I00–I78	F

Data sources:

A	U.S. Department of Health, Education, and Welfare (1956)
B	National Center for Health Statistics (2005)
C	National Center for Health Statistics (2004*a*)
D	National Center for Health Statistics (2004*b*)
E	National Center for Health Statistics (2000)
F	National Center for Health Statistics (2009)

References

Azambuja, Maria Inês and Richard Levins. 2007. "Coronary heart disease (CHD) — one or several diseases?" *Perspectives in Biology and Medicine* 50(2):228–242.

Barker, D. J. P. 1990. "The fetal and infant origins of adult disease." *British Medical Journal* 301(6761):1111.

Barker, D. J. P. and C. Osmond. 1986. "Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales." *Lancet* 327(8489):1077–1081.

Barker, D. J. P., C. Osmond, P. D. Winter, B. Margetts, and S. J. Simmonds. 1989. "Weight in infancy and death from ischaemic heart disease." *Lancet* 334(8663):577–580.

Derrick, V. P. A. 1927. "Observations on (1) errors of age in the population statistics of England and Wales, and (2) the changes in mortality indicated by the national records [with discussion]." *Journal of the Institute of Actuaries* 58:117–159.

Frost, Wade Hampton. 1939. "The age selection of mortality from tuberculosis in successive decades." *American Journal of Hygiene* 30-§A(3):91–96.

Goodman, Leo A. and Yehuda Grunfeld. 1961. "Some nonparametric tests for comovements between time series." *Journal of the American Statistical Association* 56(293):11–26.

Grmek, Mirko D. 1969. "Préliminaires d'une étude historique des maladies." *Annales. Économies, Sociétés, Civilisations* 24(6):1473–1483.

———. 1989. *Diseases in the ancient Greek world*. Johns Hopkins University Press, Baltimore. Orig. publ. 1983 as *Les Maladies à l'aube de la civilisation occidentale*. Trans. by Mireille Muellner and Leonard Muellner.

Hobcraft, John, Jane Menken, and Samuel Preston. 1982. "Age, period, and cohort effects in demography: A review." *Population Index* 48(1):4–43.

Kermack, W. O., A. G. McKendrick, and P. L. Mckinlay. 1934. "Death-rates in Great Britain and Sweden: Some general regularities and their significance." *Lancet* 223(5770):698–703.

Kuh, Diana and George Davey Smith. 1993. "When is mortality risk determined? Historical insights into a current debate." *Social History of Medicine* 6(1):101–123.

Marmot, Michael. 1992. "Coronary heart disease: Rise and fall of a modern epidemic." In Michael Marmot and Paul Elliott (eds.), *Coronary heart disease epidemiology: From aetiology to public health*, chap. 1, pp. 3–19. Oxford University of Press, Oxford.

Merrell, Margaret. 1947. "Time-specific life tables contrasted with observed survivorship." *Biometrics* 3(3):129–136.

National Center for Health Statistics. 2000. "Death rates for 72 selected causes, by 10-year age groups, race, and sex: United States, 1979–98." `http://www.cdc.gov/nchs/data/statab/gm290-98.pdf`. Date accessed: 21 March 2013.

———. 2004*a*. "Death rates for 60 selected causes, by 10-year age groups, race, and sex: United States, 1960–67." http://www.cdc.gov/nchs/data/dvs/mx196067.pdf. Date accessed: 21 March 2013.

———. 2004*b*. "Death rates for 69 selected causes, by 10-year age groups, race, and sex: United States, 1968–78." http://www.cdc.gov/nchs/data/dvs/mx196878.pdf. Date accessed: 21 March 2013.

———. 2005. "Death rates for 64 selected causes, by 10-year age groups, race, and sex: United States, 1950–59." http://www.cdc.gov/nchs/data/dvs/mx1950_59.pdf. Date accessed: 21 March 2013.

———. 2009. "Death rates for 113 selected causes, by 10-year age groups, race, and sex: United States, 1999–2006." http://www.cdc.gov/nchs/data/dvs/MortFinal2006_Worktable290r.pdf. Date accessed: 21 March 2013.

Nieto, F. Javier. 1998. "Infections and atherosclerosis: New clues from an old hypothesis?" *American Journal of Epidemiology* 148(10):937–948.

Noymer, Andrew and Michel Garenne. 2000. "The 1918 influenza epidemic's effects on sex differentials in mortality in the United States." *Population and Development Review* 26(3):565–581.

U.S. Department of Health, Education, and Welfare. 1956. "Death rates by age, race, and sex. United States, 1900–1953: Selected Causes." Vital Statistics – Special Reports 1–31, National Office of Vital Statistics, Washington DC.